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This study explored whether microscopic magnetic resonance imaging (MRI) could help determine the nature of suspicious breast lesions. After mammography identifies a suspicious lesion, there is currently no reliable, noninvasive way to determine whether the lesion is malignant, which results in unnecessary biopsies. In this study, we developed a special set-up, to be used in a GE Signa 1.5T magnet. The breast was gently compressed and small receiver coils were used to detect the MR signal to produce very high resolution images of the breast lesions. Using these coils, as well as a contrast agent, several types of images were obtained for all patients. There were 10 patients, all of whom underwent biopsies, and the biopsy results were compared with the acquired images.

The resolution was sufficient to be able to characterize the structure of the lesions. The most significant difference between the two types of lesions was the border appearance of each lesion. Benign lesions had smooth edges and malignant lesions had infiltrating edges. Very high resolution MRI could help to diagnose suspicious lesions and reduce the number of unnecessary biopsies.

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Elias A. Zerhouni 12/15/97

PI - Signature Date

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INTRODUCTION

In our original submission, we proposed to develop and test a method of localized high spatial and temporal resolution MR imaging of breast lesions applicable to humans. Our method would also permit the guidance of biopsy needles to selected lesion(s). The rationale behind our proposal was that current observed trends in the clinical management of breast cancer indicate that existing imaging methods do not provide sufficient information to improve the detection, diagnosis, and management of breast cancer. After mammography identifies a suspicious lesion, there is currently no reliable, noninvasive way to determine whether the lesion is malignant, which results in unnecessary biopsies.

The evaluation of undisturbed lesion architecture, an important histological criterion for lesion characterization, is impossible with minimally invasive needle biopsy techniques. The level of resolution of our technique was designed to increase the specificity of imaging assessment by providing unique histological characteristics.including ductal morphology and lesion/duct relationhips, microcalcification assessment (using T2* sensitive sequences), and local lymphatic and vascular architecture. Our belief was that these characteristics may alone, or in combination with needle biospy (which can be performed at the same time through the same device), might provide better classification of lesions and enhance diagnostic yield.

BACKGROUND

Imaging with low dose film-screen mammography is the currently recommended method of choice for the early detection of nonpalpable breast cancer.in women over age 40. The use of mammography has dramatically increased over the past ten years and approximately 35 to 40% of the eligible population undergoes mammographic screening. It is estimated that, barring a significant advance in cancer screening methods, the number of mammographic studies is likely to double over the next few years with a greater percentage of eligible patients being screened.

Despite the high sensitivity of mammography, up to 9% of palpable cancers show no corresponding imaging abnormality. Furthermore, with mammography, small cancers are often obscured by dense fibroglandular tissue. Another major limitation of mammography is its lack of specificity wich has led to a marked nationwide increase in the number of surgical excisions for benign disease. It is estimated that 80 to 90% of surgical breast explorations and excisions are now performed for benign disease at a direct cost estimated at 3 to 4 billion dollars annually.

In addition, the apparent incidence of breast cancer has increased at a rate of approximately 3% per year since 1980 from 84.8 to 109.5 per 100,000, leading to an ever increasing number of surgical procedures for both benign and malignant conditions. Despite the apparent increasing incidence of breast cancer, the overall mortality for this disease remains constant. Whether this phenomenon represents the effects of earlier detection, better treatment methods, or changing diagnostic thresholds used for. the earlier stages of breast cancer is unclear.

These changing patterns of clinical breast cancer have also led to modifications of the diagnostic approach to the suspicious but uncharacterized breast lesion, primarily with the development of image-guided needle biopsy methods. In parallel, more conservative and tissue sparing therapies with reduced morbidity and mortality have been advocated and implemented to better adapt the agressiveness of the therapeutic intervention to the stage of evolution and malignant potential of the cancerous lesion.

BODY

Specifically, we proposed that in vivo MR microscopy could help to better assess known imaging features as well as permit the evaluation of new features such as, for example, the mammary ducts from which cancer arises, the time-resolved pattern of contrast distribution, and the capillary density in or near lesions. In addition, using blood level oxygen-dependent (BOLD) contrast mechanisms, new parameters can also be assessed, such as tissue oxygenation heterogeneity which is known to be higher in malignancies.

Patients and Methods

Our patient population consisted of 10 female patients (average age, 48 years; range, 34-61 years) who had suspicious lesions demonstrated with mammography and/or with clinical examination for which biopsy was planned. All patients underwent core biopsy or excisional biopsy of the suspicious lesion within 2 weeks of the breast MR imaging studies. The data from two patients were obtained during the process of adjustment and optimization of the coil; hence, this data was excluded from the analysis.

MR Imaging Procdedure

All studies were performed on a 1.5T MR unit (Horizon, GE Medical Systems, Milwaukee, WI). Our initial eforts were primarily directed toward optimizing the coil design to obtain high spaital and temporal resolution. As a result, a switchable coil aray for MR microimaging of breast lesions was designed. With this switchable coil array, we were able to increase the resolution to 100x100x3,000 microns. The coil combines 12 separate microcoils, pairs of which are coupled as phased arrays. A very high resolution was obtained for any localized region of the breast, without repositioning the coil after scout imaging.

Imaging Protocol

Patients were imaged in the prone position. Sagittal spin echo T1-weighted images (TR=400ms, TE=4.4ms, 256x192 matrix, 8 cm FOV, 3 mm section thickness, interesection gap=0.5 cm, and 2 excitations), and sagittal fast spin echo T2-weighted images (TR=4000ms, TE=90ms, fat saturation, 3 mm section thickness and intersection gap of 0.5 cm, and 2 excitations) were obtained. A dynamic study was obtained in 7 patients and consisted of 3 to 5 contiguous 5 mm thick sections centered on the lesion, using a fast multiplanar spoiled gradient recalled echo sequence (FMPSPGR) (TR=51ms, TE=4.4 ms, flip angle=60°, 256x192, 1 NEX fat saturation). After precontrast images were obtained, an intravenous bolus injection of Gadopentate dimeglumine (Magnevist, Berlex Laboratories, Wayne, NJ) at 0.1 mmol/kg of body weight was administered. Images were obtained at 10-13 second intervals beginning immediately after the injection of the contrast media for 5 minutes.

MRI analysis was performed by two radiologists unaware of the histological diagnosis. Qualitative analysis was performed to assess detection of the lesion, signal intensity, margins, and pattern of enhancement. Contrast agent uptake and distribution was analyzed within regions of interest (ROI) in the area of maximum enhancement in the lesion, as determined by visual inspection of the dynamic MR images. The ROI with the maximum amplitude of enhancement was used to determine the time intensity curves. Time-intensity curves for the lesions were normalized by dividing by the precontrast signal intensity (SI) and were fitted to the following three-parameter model (1): $SI=1+A[1-\exp(-t/Tc)]-Ct$, where A is the enhancement amplitude, Tc is the time constant for arival of contrast material, C is the first order washout rate, and t is the time after injection.

RESULTS

Of eight detected lesions, four were malignant (3 ductal invasive carcinomas, 1 tubular invasive carcinoma) and 4 were benign (1 fibroadenoma, 1 intraductal papilloma, 1 fibrocystic change, 1 abscess). Examples of images typically obtained in our study are shown below.

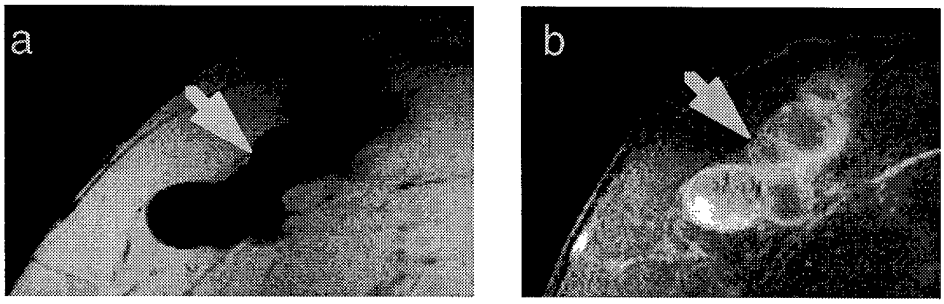

Figure 1(a) precontrast and (b) post contrast high resolution T1-weighted images obtained from a fibroadenoma demonstrating smooth margins. Images were obtained with TR= 300ms, TE= 11ms, field of view (FOV) = 8 cm, 256 x 256 matrix, slice thickness 2.5 mm, 300 μm in-plane resolution.

Figure 2: High resolution T1-weighted image obtained from an invasive ductal carcinoma showing spiculation of margins. TR=300ms, TE=11ms, FOV = 8 cm, 256 x 256 matrix, slice thickness 3.5 mm, 300 μm in-plane resolution.

All lesions could be detected on all pulse sequences except for one case that demonstrated microcalcifications on mammography and represented fibrocystic changes pathologically. All carcinomas demonstrated spiculated (n=3), or irregular (n=1) margins (see Figure 2). The fibroadenoma showed well-circumscribed borders (see Figure 1). The abscess and the intraductal papilloma demonstrated slightly irregular margins, with a questionable location along a duct for the papilloma.

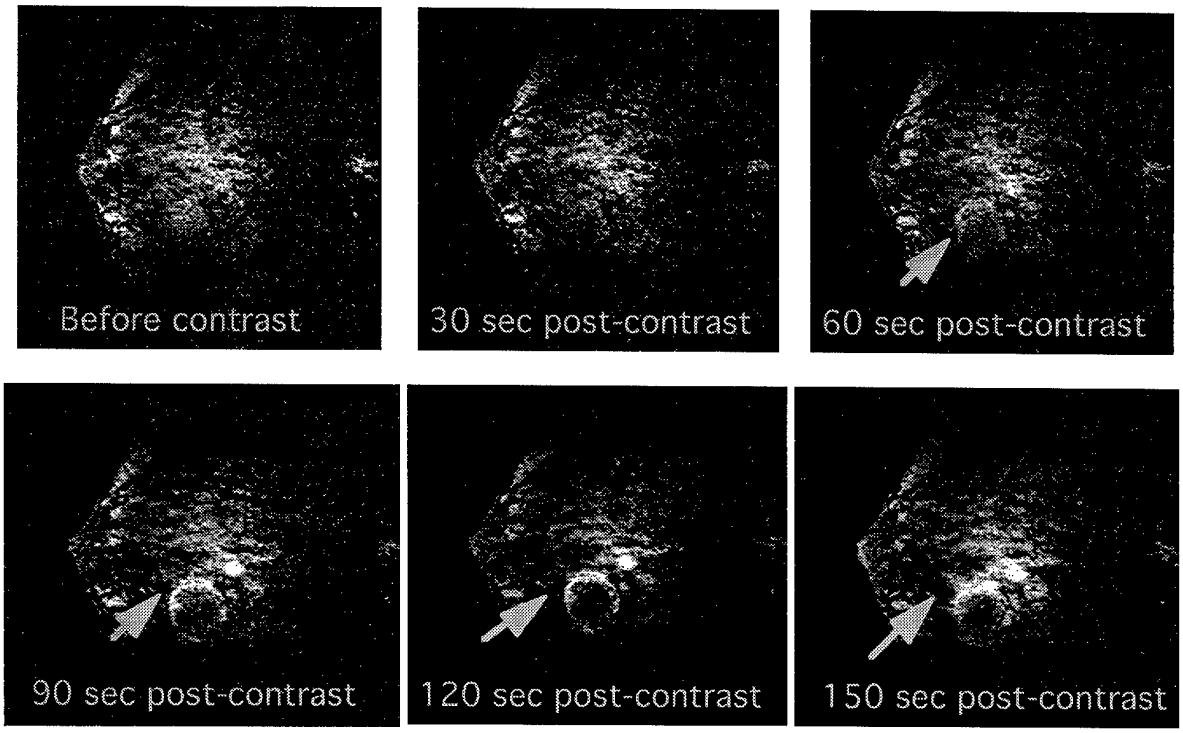

Figure 3. Enhancement pattern in an invasive ductal carcinoma with a necrotic component. Images were obtained with TR=3ms, TE=1.8ms, FOV=8cm, 256x256 matrix, 300 μm in-plane resolution, 5 mm slice thickness, 0.1mmol/kg GdDTPA, Fast spoiled gradient-echo sequence, fat saturation, number of averages =1.

All the lesions had low signal on T1- and T1-weighted images, except for one carcinoma and the fibroadenoma that demonstrated high signal on T2-weighted images. An example of the enhancement pattern for an invasive ductal carcinoma is shown in Figure 3. Heterogeneous enhancement was present in 2 carcinomas, and in 2 benign lesions. Rim enhancement that was slightly irregular on the peripheral border was seen in one of the carcinomas. We observed no significant difference between malignant and benign lesions in the rate of uptake, amplitude, or washout of the contrast.

DISCUSSION

The in-plane resolution of 300 microns achieved here was adequate for detection of the microarchitectural features of breast tissue, including ductal structures, and, therefore, for morphological characterization of breast lesions. The most conspicuous differences between benign and malignant lesions in our study were in the margins; benign lesions showed more regular margins. Results obtained so far suggest that very high resolution MRI may be useful in diagnosis of suspicious lesions. Contrast-enhanced dynamic MR studies can be performed with high temporal resolution without compromising spatial resolution. Lesion morphologic characteristics with microscopic MR imaging may be one component of a multivariate analysis to predict benign versus malignant lesions.

Our tests on coil design showed that there was neglible coupling when the coil diameter was less than the distance of separation between the paired coils. (We did not pursue a gradient coil

design because after submission of the grant application, we received an upgrade of gradient coils from GE Medical Systems that allowed us to image with 100 μm in-plane resolution. Therefore, we decided that a gradient coil design was not necessary.) We tested the original design idea of placeing two small size coils in a phased array combnination next to the compressed breast (Atalar, 1995). Although SNR was adequate and there was no appreciable signal loss due to coupling between the two coils, the design was not suitable for many applications because of the difficulty in localizing these coils correctly. As an alternative, we designed a switchable 12-coil element system which was designed to operate two at a time. In this design, we did not need to reposition the coils. The task was to find the coil pair that was closest to the target tissue. This system improved patient comfort and also decreased the total scan time significantly. The spatial resolution was dictated by the limitations of signal to noise ratio for in vivo imaging, even with specially designed phased array coils. In-plane resolution of 100 μm was achievable, but due to partial volme effects and motion blurring, we decided to use 300 μm resolution. In our experience, we have found that 300 μm in-plane resolution gives sufficient information about lesion morphology. Resolution was sufficient, however, to characterize the structure of the lesions. We found that the most significant difference between the two types of lesions was the appearance of the borders of each lesion. Benign lesions had smooth edges and malignant lesions had infiltrating edges.

We did not encounter any significant problems in accomplishing the studies. Our initial coil design provided excellent signal to noise but required frequent repositioning of the patient which increased the duration of the examination and patient discomfort. We therefore redesigned the coil and the new design is very versatile in its ability to localize on the lesion irrespective of its location without repositioning the patient.

CONCLUSIONS AND RECOMMENDATIONS

As stated in our Statement of Work, we developed a local rf coil system and achieved high resolution MR imaging of suspicious breast lesions. The resolution was sufficient to be able to characterize the structure of the lesions.

In our Specific Aims, we proposed testing our method on tissue samples and a small pilot group of patients. Our pilot group consisted of 10 patients, all of whom underwent biopsy. We were able to characterize the various types of lesions according to morphological features. The most significant difference between the two types of lesions was the border appearance of each lesion. Benign lesions had smooth edges and malignant lesions had infiltrating edges. However this observation should be confirmed with a larger patient population. In terms of evaluating capillary density, we are awaiting histological analysis of the specimens to compare with the MRI images.

In summary, we conclude that very high resolution MRI may help diagnose suspicious lesions and reduce the number of unnecessary biopsies.

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